

Current Literature in Pediatric Psychosomatics (CLiPPs)

CLiPPs: A Review of Delirium in Children After Cardiac Bypass Surgery

Patel AK, Biagas KV, Clarke EC, *et al.* Delirium in children after cardiac bypass surgery. *Pediatr Crit Care Med.* 2017;18(2):165-171.

Reviewed by: Amanda Schlesinger, MD, PGY-5, Boston Children's Hospital, Boston, MA.

Background and Objectives: Delirium is a frequent complication of cardiac bypass surgery in adult and pediatric populations, with one recent prospective study finding delirium in 30% of an adult cohort after bypass surgery. However, there have not been systematic studies of incidence of delirium after bypass in a pediatric population, impacting the ability to recognize risk factors and develop prevention strategies. This prospective, observational study was designed to describe the incidence in a single pediatric cardiothoracic ICU (PCICU).

Methods: Patients were eligible if under 21 years of age and admitted to the PCICU after cardiothoracic surgery with bypass pump usage. 194 patients ranging in age from 1 day old to 21 years old screened once per nursing shift with the Cornell Assessment of Pediatric Delirium (CAPD) instrument by nursing staff trained in the instrument. Patients were not scored if they were comatose and unarousable to verbal stimuli. Developmentally delayed patients were scored as delirious if their CAPD score >9 and neurological functioning was not at baseline. Baseline patient characteristics and intraoperative variables were also measured.

Results: 49% of patients in the sample experienced delirium during their PCICU stay. 1342 patient-days were scored and 1.4% of days were not scored due to missed screenings. Patients experienced a mean of 2 delirious days. Delirium was most often detected on days 1-3 post-operatively. Baseline risk factors associated with development of delirium were: age <2 years, cyanotic heart disease, developmental delay, albumin <3 mg/dL (used as a marker of poorer nutritional status), higher RACHS-1 (Risk Assessment for Congenital Heart Surgery) score, and above-median PIM-2 (Pediatric Index of Mortality 2) score. Clinical factors associated with delirium were: longer bypass time, coma during PCICU stay, physical restraints, use of opiates or benzodiazepines for sedation, and need for respiratory support or vasopressors. A 60% increase in PCICU length of stay was associated with delirium.

Conclusion/Commentary: The study cohort developed delirium at rates similar to adult populations, demonstrating that children undergoing cardiopulmonary bypass are highly susceptible to development of delirium, and universal screening and prevention should be considered. Findings point to preoperative vulnerabilities as a significant contributor. A limitation that may have decreased detection of delirium was that daily assessments did not assess patients overnight suggesting under-capturing of delirium rates in this population. While causality was not established, identified delirium risk factors may be candidates for interventional studies. This was a single-institution study and the authors suggest that a multi-center prospective study should be conducted to replicate these findings.

Take Away

This prospective study showed half of its patients undergoing cardiac bypass developed delirium, which was correlated with a significant increase in length of stay. Several demographic and clinical variables were associated with delirium that warrant scrutiny in risk assessment. Moreover, this study provides compelling data showing need for more awareness of and screening for delirium in a subspecialized patient population. More subspecialty delirium studies should be done to increase awareness and reduce complacency in our medical colleagues.

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CLiPPs: Hydrocortisone as an Intervention for Dexamethasone-Induced Adverse Effects in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL): Results of a Double-Blind, Randomized Controlled Trial

Hochhauser CJ, Lewis M, Kamen BA, Cole PD. Steroid-induced alterations of mood and behavior in children during treatment for acute lymphoblastic leukemia. *Support Care Cancer.* 2005;13:967-74.

Reviewed by: Meredith MacGregor, MD, Memorial Sloan Kettering Cancer Center

Background: Corticosteroids, including dexamethasone, are integral to the treatment of leukemia in children. Neuropsychological adverse effects of these

medications can significantly impact quality of life in ALL and potentially put patients in danger of physical harm. Previous studies have found benefit of anti-psychotics or benzodiazepines in mediating these effects, but these medications are not always effective and carry risk of potentially harmful side effects. The authors of this study cite recent research elucidating the pathophysiology of dexamethasone-related neuropsychological adverse effects. Specifically, that dexamethasone-induced cortisol depletion of the mineralocorticoid receptor in the brain may be the cause of these symptoms. They designed this double-blind, randomized controlled trial with a crossover design to test the utility of hydrocortisone as a treatment for some of the adverse neuropsychological and metabolic adverse effects of dexamethasone in pediatric leukemia patients.

Methods: Eligible patients were 3-16 years old, diagnosed with ALL, being treated on a medium-risk protocol (Dutch Childhood Oncology Group ALL-10 or ALL-11) that included 5-day dexamethasone pulses during the maintenance phase of treatment. The study interval included two sequential courses of dexamethasone and patients were randomly assigned to receive hydrocortisone during either the first or the second course of dexamethasone and placebo in the other. Hydrocortisone was dosed based on body surface area three times a day: 5, 3, and 2mg/meter squared. The primary outcome measure was the Strengths and Difficulties Questionnaire in Dutch (SDQ-Dut) which has 5 subscales: emotional symptoms, conduct problems, hyperactivity and inattention, peer relationship problems, and prosocial behavior. Patients were also monitored with questionnaires to track sleep, eating behavior, and physical activity, and completed neurocognitive tests on the first and last day of the steroid course. Physical monitoring included height, weight, waist-hip circumference, blood pressure, and blood work (lipid profiles, glucose, and insulin).

Results: There were no adverse effects that were attributable to hydrocortisone in either group. 46 patients completed the questionnaires at all 4 time points and 16 had a “clinically relevant” increase in psychosocial difficulties, which was defined as an increase of 5 in their

SDQ-Dut total difficulties score. In these 16 patients, the authors found that hydrocortisone had an effect on the total difficulties score, bringing the score at the end of the dexamethasone course to within a normal range. Similarly, hydrocortisone did not improve sleep rating scores overall, but in the subset of patients who had clinically relevant sleep disturbance with dexamethasone, the addition of hydrocortisone decreased the severity of this disturbance. Hydrocortisone did not have any effect on the physical parameters that they were monitoring.

Conclusion/Commentary: This study confirms past research that not all patients are equally impacted by adverse effects of corticosteroids. The findings suggest that those patients who are more affected may benefit from physiologic doses of hydrocortisone, a treatment without significant side effects. The fact that hydrocortisone did not improve metabolic adverse effects of hydrocortisone and suggest that these effects may have a different pathophysiology – an idea that could also inform further studies to help better understand the mechanism of the adverse effects of corticosteroids. The authors recommend further study focused on patients with symptoms related to dexamethasone to confirm effects of this intervention. However, the study did not include a discussion of the most severe neuropsychiatric effects – acute mania or psychosis – and when a trial of hydrocortisone could still be considered in these patients in addition to or instead of an antipsychotic. Finally, this study included only patients who were being treated on medium-risk protocols. Patients treated on high risk protocols receive more neurotoxic agents as well as higher and more frequent dosing of dexamethasone, so it is unclear if hydrocortisone would be useful in management of neuropsychiatric side effects in these patients.

Take Away

Hydrocortisone seems to be a low-risk intervention that may alleviate some of the neuropsychiatric side effects of dexamethasone and could have the potential to improve quality of life in children and adolescents being treated for some types of leukemia. However, more studies are needed and it is unclear if there is a role for this medication in patients who develop severe neuropsychiatric side effects.

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CLiPPs: Self-Management Measurement and Prediction of Clinical Outcomes in Pediatric Transplant

Annunziato RA, Bucuvalas JC, Yin W, *et al.* Self-management measurement and prediction of clinical outcomes in pediatric transplant. *J Pediatrics.* 2018;193:128-133.

Reviewed by: Alison Manning, MD, Duke University Medical Center

Background: It is well established that the period of transition from pediatric to adult healthcare is a time of vulnerability associated with declines in adherence and morbidity. It has been theorized that enhancing patient self-management skills may improve compliance and facilitate healthcare transition thus leading to improved clinical outcomes. The Responsibility and Familiarity with Illness Survey (REFILS) is a checklist of skills that has been used to quantify and track self-management levels over time. It demonstrated reliability and validity in single site studies but has lacked correlation

with medical outcomes. The authors of this multi-site, prospective cohort study sought to further develop the REFILS through correlation with biological and clinical measures to evaluate association with non-adherence and rejection in pediatric liver transplant recipients.

Methods: Participants were 400 children ages 1-17 years and their families from 5 pediatric liver transplant centers enrolled in The Medication Adherence in Children Who Had a Liver Transplant (MALT) cohort. They were followed for 2 years, and the REFILS was administered to dyads at baseline in patients 9 years of age or older and their parents. A total score as well as a “discrepancy” score (the difference between patient and parent reports of patient’s self-management) were calculated.

The REFILS examines two self-management domains in patients and parents’ perceptions about their children: perceived knowledge about illness, and responsibility for medical management. Higher scores equal greater reported self-management. Medical outcomes were measured using the Medication Level Variability Index (MLVI) which is the degree of variation in blood levels of the patients’ primary immunosuppressive agent, Tacrolimus. A higher MLVI denotes more fluctuation in levels and more erratic adherence. The main clinical outcome was biopsy-defined rejection as determined by 2 independent pathologists.

Results: 213 parent-patient dyads completed the REFILS. There were no significant associations between any demographic variables and scores except for parent level of education. REFILS scores increased with patient age as expected. Patients who reported greater self-management had lower adherence ($r=0.26$, $P<.01$). Greater discrepancy between patient and parent report was associated with lower adherence; when patients endorsed higher levels of self-management than their parent reported for them, it was associated with higher MLVI poorer adherence ($r=0.20$, $P<.01$). Patient REFILS scores predicted non-adherence and future rejection (26.1 (SD 4.2) vs 23.7 (SD 4.8)). Discrepancies between patient and parent report were larger for those who experienced rejection (1.6 (SD 4.2) vs 0.01 (SD 4.2)).

Conclusion/Commentary: Patients who reported a higher degree of self-management had worse clinical outcomes. This study echoes other pediatric transplant literature cautioning the transition of responsibility from the parent/caregiver to the patient may be ill-advised if poorly timed, and that a gradual and thoughtful transfer of accountability is essential and must be individualized.

Greater discrepancy between child/adolescent and parent self-management scores was also associated with poor adherence and rejection and is a novel approach to evaluating transition readiness. This discrepancy may reflect a basic level of communication discord in the home which is known to negatively impact adherence. This measure may be a useful tool to facilitate and inform conversations about adherence and allocation of caregiver and patient responsibility. This paper highlights why adolescent self-report must not be taken as the sole indicator of adherence and readiness for transition.

Take Away

The REFILS may be a useful tool to aid in recognizing patients at risk for poor adherence and transplant rejection, and to prompt conversations between providers and parent-child dyads about the importance of continued parent involvement and thoughtful transition of responsibility. Patient reports of high self-management and parent and child discrepancies between the child’s self-management may be helpful warnings about the need for intervention in adherence and prevention of transplant rejection.

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